SEQUENCE LISTING AP20 Rec'd PCT/PTO 26 MAY 2006

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         Harder, Friedrich

<120>   Method for Preventing and Treating Diabetes Using DG119

<130>   2923-757

<150>   PCT/EP04/013535
<151>   2004-11-29

<150>   EP 03 027 514.3
<151>   2003-11-28

<160>   13

<170>   PatentIn version 3.3

<210>   1
<211>   719
<212>   PRT
<213>   Danio rerio

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Met Thr Glu Met Lys Ile Trp Cys Val Leu Leu Met Ala Phe Ala Leu
1   5   10   15

Thr Ser Ala Ala Pro Lys Ser His Leu Arg Leu Glu Glu Lys Thr Lys
            20   25   30

Asp Asn Asn Asp Thr Leu Gln Val Glu Ile Asp Asn Gln Glu His Ile
            35   40   45

Leu Ser Gln Leu Leu Gly Asp Tyr Asp Lys Val Lys Ala Leu Ser Glu
    50   55   60

Gly Ser Asp Cys Gly Cys Lys Cys Val Val Arg Pro Leu Ser Ala Ser
65   70   75   80

Ala Cys Gln Arg Ile Arg Glu Gly His Ala Thr Pro Gln Asp Phe Tyr
                85   90   95

Thr Val Glu Thr Ile Thr Ser Gly Pro His Cys Lys Cys Ala Cys Ile

1

Ala Pro Pro Ser Ala Leu Asn Pro Cys Glu Gly Asp Phe Arg Leu Lys
        115   120   125

Lys Leu Arg Gln Ala Gly Lys Asp Asn Ile Lys Leu Ser Thr Ile Leu
        130   135   140

Glu Leu Leu Glu Gly Ser Phe Tyr Gly Met Asp Leu Leu Lys Leu His
145   150   155   160

Ser Val Thr Thr Lys Ile Leu Asp Arg Met Asp Thr Ile Glu Lys Met
                165   170   175

Val Leu Asn Asn Gln Thr Glu Glu Lys Leu Asn Thr Ile Ser Thr Ser
            180   185   190

Pro Asn Pro Gln Leu Ser Thr Ser Ser Pro Thr Thr Leu Pro Ser Val
        195   200   205

Ile Gln Glu Lys Ser Thr Ser Leu Arg Gln Gln Asn Asp Glu Ala Ala
    210   215   220

Ala Phe Gln His Met Glu Ser Lys Tyr Glu Glu Lys Phe Val Gly Asp
225   230   235   240

Ile Leu Asn Ser Gly Ser Asp Leu Asn Lys Ala Thr Thr Ala Leu Gln
            245   250   255

Glu Gln Glu Gln Gln Gly Arg Lys Lys Gln Pro Lys Ile Thr Val Arg
            260   265   270

Gly Ile Thr Tyr Tyr Arg Ser Asp Pro Val Asp Glu Met Asp Ser Glu
        275   280   285

Lys Asn Leu Lys Glu Thr Ser Ala Ser Ser Val Thr Gln Thr Gly Ala
        290   295   300

Leu Ile Lys Glu His Leu Lys Ala Ser Thr Gln Ser Thr Leu Asn Thr
305   310   315   320

Leu Thr Pro Ser Pro Thr Ser His Ser Asn Ala Leu Thr Val Thr Glu
            325   330   335

Ser Ser Val Gly Ile Asn Ala His Lys Gly Glu Val Thr Thr Ile Val
            340   345   350

Met Thr Ala Ser Val Thr Gly Ser Lys Thr Asp Ser Val Thr Asp Leu
            355   360   365

Thr Gln Leu Ser Pro Arg Val Arg Glu Thr Leu Thr Thr Thr Arg Thr
    370   375   380

Thr Thr Lys Thr Ala Thr Thr Ser Gln Pro Val Lys Arg Lys Tyr Ser
385   390   395   400

Ile Ser Trp Asp Glu Glu Glu Glu Ala Val Val Pro Glu Gln Val Glu
            405   410   415

Glu Glu Lys Ala Val Lys Pro Val Val Glu Asp Lys Val Gly Glu Glu
            420   425   430

Pro Gln Arg Lys Pro Gly Thr Ala His His Gln Ala Lys Thr Ile Ser
    435   440   445

Thr Val Lys Gln Gln Ile Lys Phe Ser Leu Gly Met Cys Lys Asp Thr
    450   455   460

Leu Ala Thr Ile Ser Glu Pro Ile Thr His Asn Thr Tyr Gly Arg Asn
465   470   475   480

Glu Gly Ala Trp Met Lys Asp Pro Leu Asp Gln Asp Asp Lys Ile Tyr
            485   490   495

Val Thr Asn Tyr Tyr Tyr Gly Asn Asn Leu Leu Glu Phe Arg Asn Ile
            500   505   510

Asp Val Phe Lys Gln Gly Arg Phe Thr Asn Ser Tyr Lys Leu Pro Tyr
            515   520   525

Asn Trp Ile Gly Thr Gly His Val Val Tyr Lys Gly Ala Phe Tyr Tyr
    530   535   540

3

```
Asn Arg Ala Phe Ser Arg Asp Ile Ile Lys Phe Asp Leu Arg Leu Arg
545             550             555             560


Tyr Val Ala Ala Trp Thr Met Leu His Asp Ala Val Phe Glu Asn Asp
                565             570             575


Asp Val Ser Ser Trp Arg Trp Arg Gly Asn Ser Asp Met Asp Leu Ala
                580             585             590


Ile Asp Glu Ser Gly Leu Trp Val Ile Tyr Pro Ala Leu Asp Asp Glu
        595             600             605


Gly Phe Leu Gln Glu Val Ile Val Leu Ser Arg Leu Asn Pro Thr Asp
    610             615             620


Leu Ser Met Lys Arg Glu Thr Thr Trp Arg Thr Gly Leu Arg Arg Asn
625             630             635             640


Arg Tyr Gly Asn Cys Phe Ile Val Cys Gly Val Leu Tyr Ala Thr Asp
            645             650             655


Ser Tyr Asn Gln Gln Asp Thr Asn Leu Ser Tyr Ala Phe Asp Thr His
            660             665             670


Thr Asn Thr Gln Val Ile Pro His Leu Pro Phe Ser Asn Asn Tyr Thr
        675             680             685


Tyr Val Thr Gln Ile Asp Tyr Asn Pro Lys Glu Arg Val Leu Tyr Ala
    690             695             700


Trp Asp Asn Gly His Gln Val Thr Tyr Asn Val Gln Phe Ala Tyr
705             710             715


<210>    2
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<212>    PRT
<213>    Danio rerio


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<222>    (198)..(198)
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Met Gly Leu Leu Leu Tyr Ile Phe Cys Cys Val Phe Cys Leu Thr Arg
1   5   10   15

Ala Asn Val Glu Gln Gln Ala Thr Asp Asn Thr Asp Asn Arg Ala Thr
            20   25   30

Leu Glu Asp Glu Met Asp Asn Gln Glu Asn Ile Leu Thr Gln Leu Ile
            35   40   45

Gly Asp Tyr Asp Lys Val Lys Thr Leu Ser Glu Gly Ser Asp Cys Gln
        50   55   60

Cys Lys Cys Val Val Arg Pro Met Ser Arg Ser Ala Cys Lys Arg Ile
65   70   75   80

Glu Glu Ala Gln Ala Lys Ile Glu Asp Phe Tyr Thr Val Glu Pro Val
            85   90   95

Thr Ala Gly Pro Asn Cys Lys Lys Cys Ala Cys Ile Ala Pro Pro Ser
            100   105   110

Ala Leu Asn Pro Cys Glu Gly Asp Phe Arg Phe Lys Lys Leu Gln Lys
        115   120   125

Thr Gly Gln Tyr Asp Ile Lys Leu Ser Asn Ile Met Asp Leu Leu Glu
    130   135   140

Glu Arg Val Asp Asn Ile Glu Lys Gly Glu Lys Gly Gln Gly Lys Gly
145   150   155   160

Ala Arg Ser Asn Gln Arg Gln Glu Lys Lys Lys Arg Leu Ser Val Val
            165   170   175

Cys Trp Ser Leu His Cys Arg Arg Thr Gln Gln Arg Leu Leu Leu Thr
            180   185   190

Leu Arg Tyr Arg Cys Xaa Ser Val Leu Glu Pro Ser Leu Gln Lys Asn
        195   200   205

```
Ala Ala Ala Ala Phe Ala His Thr Glu Val Gln Met Gln Gln Phe Ile
    210             215             220

Pro Asp Gln Arg Lys Tyr Glu Glu Lys Phe Val Gly Asn Gln Gly Pro
225             230             235             240

Ser Lys Pro Val Leu Lys Lys Ser Lys Ser Glu Gly Gln Glu Glu Gln
                245             250             255

His Lys Pro Ala Lys Thr Lys Ala Asp Ala Lys Asn Met Ser Leu Arg
            260             265             270

Ser Met Thr Phe Tyr Lys Ala Asn Arg Met Glu Asp Ser Glu Gly Glu
        275             280             285

Glu Arg Asp Leu Ile Ile Glu Asp Gln Leu His Lys Gln Gly Leu Asn
    290             295             300

Thr Pro Val Thr Thr Pro Glu Ala Thr Val Thr Val Thr Gln Ser Thr
305             310             315             320

Thr Ile Asn Leu Asn Thr Gln Asn Phe Thr Thr Ala Arg Met Ser Asn
            325             330             335

Val Thr Lys Gln Thr Gln Gly Gln Ser Val Lys Ala Met Met Ser Ser
            340             345             350

Thr Ile Thr Thr Glu Arg Pro Thr Met Pro Thr Ser Thr Thr Ser Thr
        355             360             365

Ser Thr Met Thr Pro Gly Thr Asn Thr Thr Thr Ile Ala Thr Pro Leu
    370             375             380

Val Val Pro Lys Gln Leu Ala Ser Val Thr Val Gly Gln Val Ser Asn
385             390             395             400

Ser Tyr Lys Leu Pro Tyr Asn Trp Ile Gly Thr Gly His Val Val Tyr
                405             410             415

Ser Gly Ser Phe Phe Tyr Asn Arg Ala Phe Ser Arg Asp Ile Ile Arg
            420             425             430
```

6

```
Phe Asp Leu Arg Leu Arg Tyr Val Ala Ala Trp Thr Thr Leu His Asp
        435                 440                 445


Ala Ile Leu Glu Glu Glu Glu Ala Pro Trp Thr Trp Gly Gly His Ser
        450                 455                 460


Asp Ile Asp Phe Ser Val Asp Glu Ser Gly Leu Trp Leu Val Tyr Pro
465                 470                 475                 480


Ala Leu Asp Asp Glu Gly Phe His Gln Glu Val Ile Ile Leu Ser Lys
                485                 490                 495


Leu Arg Ala Ser Asp Leu Gln Lys Glu Lys Ser Trp Arg Thr Gly Leu
                500                 505                 510


Arg Arg Asn Tyr Tyr Gly Asn Cys Phe Val Ile Cys Gly Val Leu Tyr
        515                 520                 525


Ala Val Asp Ser Phe Glu Arg Thr His Ala Asn Ile Ser Tyr Ala Phe
        530                 535                 540


Asp Thr His Thr His Thr Gln Met Ile Pro Arg Leu Pro Phe Ile Asn
545                 550                 555                 560


Asn Tyr Thr Tyr Thr Thr Gln Ile Asp Tyr Asn Pro Lys Glu Arg Met
                565                 570                 575


Leu Tyr Ala Trp Asp Asn Gly His Gln Val Thr Tyr Asp Val Ile Phe
                580                 585                 590


Ala Tyr


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<213>   Danio rerio

<400>   3

Met Trp Arg Ile Val Glu Leu Val Ala Cys Leu Leu Met Met Ser Ser
1                   5                   10                  15
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7

His Val Ser Ser Gln Ser Lys Ile Phe Gly Glu Glu Gln Val Arg Met
            20   25   30

Thr Ser Glu Gly Ser Asp Cys Arg Cys Lys Cys Ile Met Arg Pro Leu
        35   40   45

Thr Arg Asp Ala Cys Ala Arg Leu Arg Thr Gly Ser Val Arg Val Glu
    50   55   60

Asp Phe Tyr Thr Val Glu Thr Val Ser Ser Gly Ala Asp Cys Lys Cys
65   70   75   80

Ser Cys Thr Ala Pro Pro Ser Ser Leu Asn Pro Cys Glu Asn Glu Trp
                85   90   95

Lys Arg Glu Lys Leu Lys Lys Gln Ala Pro Glu Leu Leu Lys Leu Gln
            100   105   110

Ser Met Val Asp Leu Leu Glu Gly Thr Leu Phe Ser Met Asp Leu Leu
            115   120   125

Lys Val His Ser Tyr Ile Asn Lys Val Val Ser Gln Met Asn Asn Leu
    130   135   140

Glu Glu
145

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<222>   (103)..(103)
<223>   Xaa can be any naturally occurring amino acid

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Met Trp Ile Tyr Ala Ser Val Leu Thr Tyr Leu Leu Leu Leu Thr Arg
1   5   10   15

Asp Ala Arg Ser Leu Ser Lys Ile Phe Gly Glu Pro Glu Pro Val Lys

8

```
            20                      25                      30

Met Ile Ser Glu Gly Ser Asp Cys Arg Cys Lys Cys Val Met Arg Pro
        35              40              45

Leu Ser Ile Glu Ala Cys Ser Arg Leu Arg Asp Gly Ser Leu Arg Val
        50              55              60

Asp Asp Phe Tyr Thr Val Glu Thr Val Ser Ser Gly Ser Asp Cys Lys
65              70              75              80

Cys Ser Cys Thr Ala Pro Pro Ser Ser Leu Asn Pro Cys Glu Asn Glu
                85              90              95

Trp Arg Thr Glu Lys Leu Xaa Lys Gln Ala Pro Glu Leu Leu Lys Leu
            100             105             110

His Ser Met Val Asp Leu Leu Glu Gly Thr Leu Tyr Ser Met Asp Leu
            115             120             125

Met Lys Val His Ala Tyr Met Asn Lys Val Val Ser Gln Met Asn Thr
    130             135             140

Leu Glu Glu Val Met Thr Ile Lys Thr Asn Leu Thr Arg Glu Asn Glu
145             150             155             160

Phe Val Arg Asp Ser Val Val Asn Leu Ser Asn Gln Leu Lys Arg Tyr
            165             170             175

Glu Asn Tyr Ser Asp Ile Met Val Ser Ile Lys Lys Glu Ile Ser Ser
            180             185             190

Leu Gly Leu Gln Leu Leu Gln Lys Asp Ala Ala Ser Asp Ser Lys Ala
            195             200             205

Gln Val Gly Thr Glu Ser Lys Lys Ser Lys Glu Ala Ile Lys Pro Pro
    210             215             220

Asn Lys Lys Pro Pro Ala Val Lys Pro Pro Pro Lys Gln Pro Lys Glu
225             230             235             240
```

9

```
Lys Pro Val Lys Pro Lys Lys Glu Ala Pro Ala Lys Ala Ala Lys Pro
                245                 250                 255


Ala Lys Pro Asp Pro Thr Thr Lys Thr Lys Thr Ser Val His Gln Thr
                260             265                 270


Gly Val Ile Arg Gly Ile Thr Tyr Tyr Lys Ala Ser Lys Ser Glu
            275                 280                 285



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Met Ala Tyr Pro Leu Pro Leu Val Leu Cys Phe Ala Leu Val Val Ala
1   5   10   15

Gln Val Trp Gly Ser Thr Thr Pro Pro Thr Gly Thr Ser Glu Pro Pro
            20   25   30

Asp Val Gln Thr Val Glu Pro Thr Glu Asp Asp Ile Leu Gln Asn Glu
            35   40   45

Ala Asp Asn Gln Glu Asn Val Leu Ser Gln Leu Leu Gly Asp Tyr Asp
        50   55   60

Lys Val Lys Ala Val Ser Glu Gly Ser Asp Cys Gln Cys Lys Cys Val
65   70   75   80

Val Arg Pro Leu Gly Arg Asp Ala Cys Gln Arg Ile Asn Gln Gly Ala
                85   90   95

Ser Arg Lys Glu Asp Phe Tyr Thr Val Glu Thr Ile Thr Ser Gly Ser
            100   105   110

Ser Cys Lys Cys Ala Cys Val Ala Pro Pro Ser Ala Val Asn Pro Cys
        115   120   125

Glu Gly Asp Phe Arg Leu Gln Lys Leu Arg Glu Ala Asp Ser Arg Asp
        130   135   140

Leu Lys Leu Ser Thr Ile Ile Asp Met Leu Glu Gly Ala Phe Tyr Gly
145   150   155   160

Leu Asp Leu Leu Lys Leu His Ser Val Thr Thr Lys Leu Val Gly Arg
                165   170   175

Val Asp Lys Leu Glu Glu Glu Val Ser Lys Asn Leu Thr Lys Glu Asn
            180   185   190

```
Glu Gln Ile Lys Glu Asp Val Glu Glu Ile Arg Thr Glu Leu Asn Lys
        195             200             205

Arg Gly Lys Glu Asn Cys Ser Asp Asn Thr Leu Glu Ser Met Pro Asp
        210             215             220

Ile Arg Ser Ala Leu Gln Arg Asp Ala Ala Ala Ala Tyr Ala His Pro
225             230             235             240

Glu Tyr Glu Glu Arg Phe Leu Gln Glu Glu Thr Val Ser Gln Gln Ile
            245             250             255

Asn Ser Ile Glu Leu Leu Arg Thr Gln Pro Leu Val Pro Pro Ala Ala
            260             265             270

Met Lys Pro Gln Arg Pro Leu Gln Arg Gln Val His Leu Arg Gly Arg
        275             280             285

Leu Ala Ser Lys Pro Thr Val Ile Arg Gly Ile Thr Tyr Tyr Lys Ala
        290             295             300

Lys Val Ser Glu Glu Glu Asn Asp Ile Glu Glu Gln His Asp Glu Leu
305             310             315             320

Phe Ser Gly Asp Ser Gly Val Asp Leu Leu Ile Glu Asp Gln Leu Leu
            325             330             335

Arg Gln Glu Asp Leu Leu Thr Ser Ala Thr Arg Arg Pro Ala Thr Thr
            340             345             350

Arg His Thr Ala Ala Val Thr Thr Asp Ala Ser Ile Gln Ala Ala Ala
            355             360             365

Ser Ser Ser Glu Pro Ala Gln Ala Ser Ala Ser Ala Ser Ser Phe Val
        370             375             380

Glu Pro Ala Pro Gln Ala Ser Asp Arg Glu Leu Leu Ala Thr Pro Gln
385             390             395             400

Thr Thr Thr Val Phe Pro Glu Pro Thr Gly Val Met Pro Ser Thr Gln
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Val Ser Pro Thr Thr Val Ala His Thr Ala Val Gln Pro Leu Pro Ala
            420   425   430

Met Val Pro Gly Asp Ile Phe Val Glu Ala Leu Pro Leu Val Pro Leu
            435   440   445

Leu Pro Asp Thr Val Gly Thr Asp Met Pro Glu Glu Glu Gly Thr Ala
            450   455   460

Gly Gln Glu Ala Thr Ser Ala Gly Pro Ile Leu Ser Pro Glu Glu Glu
465   470   475   480

Asp Asp Ile Arg Asn Val Ile Gly Arg Cys Lys Asp Thr Leu Ser Thr
                  485   490   495

Ile Thr Gly Pro Thr Thr Gln Asn Thr Tyr Gly Arg Asn Glu Gly Ala
            500   505   510

Trp Met Lys Asp Pro Leu Ala Lys Asp Asp Arg Ile Tyr Val Thr Asn
            515   520   525

Tyr Tyr Tyr Gly Asn Thr Leu Val Glu Phe Arg Asn Leu Glu Asn Phe
            530   535   540

Lys Gln Gly Arg Trp Ser Asn Ser Tyr Lys Leu Pro Tyr Ser Trp Ile
545   550   555   560

Gly Thr Gly His Val Val Tyr Asn Gly Ala Phe Tyr Tyr Asn Arg Ala
            565   570   575

Phe Thr Arg Asn Ile Ile Lys Tyr Asp Leu Lys Gln Arg Tyr Val Ala
            580   585   590

Ala Trp Ala Met Leu His Asp Val Ala Tyr Glu Glu Ala Thr Pro Trp
            595   600   605

Arg Trp Gln Gly His Ser Asp Val Asp Phe Ala Val Asp Glu Asn Gly
            610   615   620

Leu Trp Leu Ile Tyr Pro Ala Leu Asp Asp Glu Gly Phe Asn Gln Glu
625   630   635   640

Val Ile Val Leu Ser Lys Leu Asn Ala Val Asp Leu Ser Thr Gln Lys
                645   650   655

Glu Thr Thr Trp Arg Thr Gly Leu Arg Arg Asn Phe Tyr Gly Asn Cys
.   660   665   670

Phe Val Ile Cys Gly Val Leu Tyr Ala Val Asp Ser Tyr Asn Gln Arg
            675   680   685

Asn Ala Asn Ile Ser Tyr Ala Phe Asp Thr His Thr Asn Thr Gln Ile
        690   695   700

Val Pro Arg Leu Leu Phe Glu Asn Glu Tyr Ser Tyr Thr Thr Gln Ile
705   710   715   720

Asp Tyr Asn Pro Lys Asp Arg Leu Leu Tyr Ala Trp Asp Asn Gly His
                725   730   735

Gln Val Thr Tyr His Val Ile Phe Ala Tyr
            740   745

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<213>   Homo sapiens

<400>   11

Met Ala Lys Pro Arg Leu Leu Val Leu Tyr Phe Ala Leu Ile Val Val
1   5   10   15

Pro Ala Trp Val Ser Ser Ile Val Leu Thr Gly Thr Ser Glu Pro Pro
            20   25   30

Asp Ala Gln Thr Val Ala Pro Ala Glu Asp Glu Thr Leu Gln Asn Glu
        35   40   45

Ala Asp Asn Gln Glu Asn Val Leu Ser Gln Leu Leu Gly Asp Tyr Asp
    50   55   60

14

```
Lys Val Lys Ala Met Ser Glu Gly Ser Asp Cys Gln Cys Lys Cys Val
65              70              75              80


Val Arg Pro Leu Gly Arg Asp Ala Cys Gln Arg Ile Asn Ala Gly Ala
                85              90              95


Ser Arg Lys Glu Asp Phe Tyr Thr Val Glu Thr Ile Thr Ser Gly Ser
            100             105             110


Ser Cys Lys Cys Ala Cys Val Ala Pro Pro Ser Ala Leu Asn Pro Cys
            115             120             125


Glu Gly Asp Phe Arg Leu Gln Lys Leu Arg Glu Ala Asp Ser Gln Asp
        130             135             140


Leu Lys Val Gly Pro Gly Met Gly Gln Cys Leu Gly Arg Glu Gly Thr
145             150             155             160


Phe Glu Ile His Lys Ser Gly Lys Ala Met Val Glu Asp Ser Lys Pro
                165             170             175


Phe Glu Glu Gly Leu Ser His Phe Leu Thr Gln Thr Phe Arg Lys Ala
            180             185             190          .


Glu Cys Thr Tyr Thr Ile Val Leu Ala Tyr Ile Pro Val Tyr Thr Asn
        195             200             205


Val Phe Leu Thr Ala Thr Ser Gln Phe Leu Ala Ser Gly Phe Pro Val
    210             215             220


Glu Pro Pro Leu Ser Thr Ile Ile Asp Met Leu Glu Gly Ala Phe Tyr
225             230             235             240


Gly Leu Asp Leu Leu Lys Leu His Ser Val Thr Thr Lys Leu Val Gly
            245             250             255


Arg Val Asp Lys Leu Glu Glu Met Leu Glu Gly Ala Phe Tyr Gly Leu
            260             265             270


Asp Leu Leu Lys Leu His Ser Val Thr Thr Lys Leu Val Gly Arg Val
        275             280             285
```

15

```
Asp Lys Leu Glu Glu Glu Val Ser Lys Asn Leu Thr Lys Glu Asn Glu
    290             295             300

Gln Ile Lys Glu Asp Met Glu Glu Ile Arg Thr Glu Met Asn Lys Arg
305             310             315             320

Gly Lys Glu Asn Cys Ser Glu Asn Ile Leu Asp Ser Met Pro Asp Ile
                325             330             335

Arg Ser Ala Leu Gln Arg Asp Ala Ala Ala Tyr Ala His Pro Glu
            340             345             350

Tyr Glu Glu Arg Phe Leu Gln Glu Glu Thr Val Ser Gln Gln Ile Asn
    355             360             365

Ser Ile Glu Leu Leu Gln Thr Arg Pro Leu Ala Leu Pro Glu Val Val
    370             375             380

Lys Ser Gln Arg Pro Leu Gln Arg Gln Val His Leu Arg Gly Arg Pro
385             390             395             400

Ala Ser Gln Pro Thr Val Ile Arg Gly Ile Thr Tyr Tyr Lys Ala Lys
                405             410             415

Val Ser Glu Glu Glu Asn Asp Ile Glu Glu Gln Gln Asp Glu Phe Phe
            420             425             430

Ser Gly Asp Asn Gly Val Asp Leu Leu Ile Glu Asp Gln Leu Leu Arg
            435             440             445

His Asn Gly Leu Met Thr Ser Val Thr Arg Arg Pro Ala Ala Thr Arg
    450             455             460

Gln Gly His Ser Thr Ala Val Thr Ser Asp Leu Asn Ala Arg Thr Ala
465             470             475             480

Pro Trp Ser Ser Ala Leu Pro Gln Pro Ser Thr Ser Asp Pro Ser Ile
                485             490             495

Ala Asn His Ala Ser Val Gly Pro Thr Leu Gln Thr Thr Ser Val Ser
            500             505             510
```

16

```
Pro Asp Pro Thr Arg Glu Ser Val Leu Gln Pro Ser Pro Gln Val Pro
    515                 520             525

Ala Thr Thr Val Ala His Thr Ala Thr Gln Gln Pro Ala Ala Pro Ala
    530             535             540

Pro Pro Ala Val Ser Pro Arg Glu Ala Leu Met Glu Ala Met His Thr
545             550             555             560

Val Pro Val Pro Pro Thr Thr Val Arg Thr Asp Ser Leu Gly Lys Asp
            565             570             575

Ala Pro Ala Gly Trp Gly Thr Thr Pro Ala Ser Pro Thr Leu Ser Pro
        580             585             590

Glu Glu Glu Asp Asp Ile Arg Asn Val Ile Gly Arg Cys Lys Asp Thr
    595             600             605

Leu Ser Thr Ile Thr Gly Pro Thr Thr Gln Asn Thr Tyr Gly Arg Asn
    610             615             620

Glu Gly Ala Trp Met Lys Asp Pro Leu Ala Lys Asp Glu Arg Ile Tyr
625             630             635             640

Val Thr Asn Tyr Tyr Tyr Gly Asn Thr Leu Val Glu Phe Arg Asn Leu
            645             650             655

Glu Asn Phe Lys Gln Gly Arg Trp Ser Asn Ser Tyr Lys Leu Pro Tyr
            660             665             670

Ser Trp Ile Gly Thr Gly His Val Val Tyr Asn Gly Ala Phe Tyr Tyr
            675             680             685

Asn Arg Ala Phe Thr Arg Asn Ile Ile Lys Tyr Asp Leu Lys Gln Arg
    690             695             700

Tyr Val Ala Ala Trp Ala Met Leu His Asp Val Ala Tyr Glu Glu Ala
705             710             715             720

Thr Pro Trp Arg Trp Gln Gly His Ser Asp Val Asp Phe Ala Val Asp
```

17

Glu Asn Gly Leu Trp Leu Ile Tyr Pro Ala Leu Asp Asp Glu Gly Phe
    740   745   750

Ser Gln Glu Val Ile Val Leu Ser Lys Leu Asn Ala Ala Asp Leu Ser
    755   760   765

Thr Gln Lys Glu Thr Thr Trp Arg Thr Gly Leu Arg Arg Asn Phe Tyr
  770   775   780

Gly Asn Cys Phe Val Ile Cys Gly Val Leu Tyr Ala Val Asp Ser Tyr
785   790   795   800

Asn Gln Arg Asn Ala Asn Ile Ser Tyr Ala Phe Asp Thr His Thr Asn
    805   810   815

Thr Gln Ile Val Pro Arg Leu Leu Phe Glu Asn Glu Tyr Ser Tyr Thr
    820   825   830

Thr Gln Ile Asp Tyr Asn Pro Lys Asp Arg Leu Leu Tyr Ala Trp Asp
   835   840   845

Asn Gly His Gln Val Thr Tyr His Val Ile Phe Ala Tyr
  850   855   860

<210> 12
<211> 681
<212> PRT
<213> Mus musculus

<400> 12

Met Glu Ala Ala Ala Val Leu Pro Arg Tyr Leu Gln Leu Arg Leu Leu
1   5   10   15

Leu Val Leu Leu Leu Leu Val Leu Leu Arg Ala Gly Pro Val Trp Pro
    20   25   30

Asp Ser Lys Val Phe Ser Asp Leu Asp Gln Val Arg Met Thr Ser Glu
    35   40   45

Gly Ser Asp Cys Arg Cys Lys Cys Ile Met Arg Pro Leu Ser Lys Asp

Ala Cys Ser Arg Val Arg Ser Gly Arg Ala Arg Val Glu Asp Phe Tyr
65   70   75   80

Thr Val Glu Thr Val Ser Ser Gly Ala Asp Cys Arg Cys Ser Cys Thr
                    85   90   95

Ala Pro Pro Ser Ser Leu Asn Pro Cys Glu Asn Glu Trp Lys Met Glu
                100   105   110

Lys Leu Lys Lys Gln Ala Pro Glu Leu Leu Lys Leu Gln Ser Met Val
            115   120   125

Asp Leu Leu Glu Gly Ala Leu Tyr Ser Met Asp Leu Met Lys Val His
    130   135   140

Ala Tyr Ile Gln Lys Val Ala Ser Gln Met Asn Thr Leu Glu Glu Ser
145   150   155   160

Ile Lys Ala Asn Leu Ser Leu Glu Asn Lys Val Val Lys Asp Ser Val
                165   170   175

His His Leu Ser Glu Gln Leu Lys Ser Tyr Glu Asn Gln Ser Ala Ile
            180   185   190

Met Met Ser Ile Lys Lys Glu Leu Ser Ser Leu Gly Leu Gln Leu Leu
            195   ·   200   205

Gln Arg Asp Ala Ala Ala Val Pro Ala Thr Ala Pro Ala Ser Ser Pro
    210   215   220

Asp Ser Lys Ala Gln Asp Thr Ala Gly Gly Gln Gly Arg Asp Leu Asn
225   230   235   240

Lys Tyr Gly Ser Ile Gln Lys Ser Phe Ser Asp Lys Gly Leu Ala Lys
                245   250   255

Pro Pro Lys Glu Lys Leu Leu Lys Val Glu Lys Leu Arg Lys Glu Ser
            260   265   270

19

```
Ile Lys Gly Arg Ile Pro Gln Pro Thr Ala Arg Pro Arg Ala Leu Ala
        275                 280             285

Gln Gln Gln Ala Val Ile Arg Gly Phe Thr Tyr Tyr Lys Ala Gly Arg
    290             295                 300

Gln Glu Ala Arg Gln Glu Ala Arg Gln Glu Ala Pro Lys Ala Ala Ala
305             310             315                 320

Asp Ser Thr Leu Lys Gly Thr Ser Trp Leu Glu Lys Leu Pro Pro Lys
                325             330                 335

Ile Glu Ala Lys Leu Pro Glu Pro Asn Ser Ala Lys His Asp Asp Val
            340             345             350

Arg Leu Gln Ala Ser Glu Gly Gly Asn Leu Thr Pro Asp Ile Thr Thr
        355             360             365

Thr Thr Thr Ser Thr Ser Ser Ser Thr Thr Thr Thr Gly Thr Thr
    370             375             380

Ser Thr Thr Ser Thr Thr Ser Thr Thr Ser Thr Thr Thr Pro Ser Pro
385             390             395             400

Ile Thr Thr Pro Trp Pro Thr Glu Pro Pro Leu His Pro Glu Val Pro
            405             410             415

Ser Gln Gly Arg Glu Asp Ser Cys Glu Gly Thr Leu Arg Ala Val Asp
            420             425             430

Pro Pro Val Lys His His Ser Tyr Gly Arg His Glu Gly Ala Trp Met
        435             440             445

Lys Asp Pro Ala Ala Leu Asp Asp Arg Ile Tyr Val Thr Asn Tyr Tyr
    450             455             460

Tyr Gly Asn Ser Leu Val Glu Phe Arg Asn Leu Glu Asn Phe Lys Gln
465             470             475             480

Gly Arg Trp Ser Asn Met Tyr Lys Leu Pro Tyr Asn Trp Ile Gly Thr
            485             490             495
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Gly His Val Val Tyr Gln Gly Ala Phe Tyr Tyr Asn Arg Ala Phe Thr
            500   505   510

Lys Asn Ile Ile Lys Tyr Asp Leu Arg Gln Arg Phe Val Ala Ser Trp
            515   520   525

Ala Leu Leu Pro Asp Val Val Tyr Glu Asp Thr Thr Pro Trp Lys Trp
            530   535   540

Arg Gly His Ser Asp Ile Asp Phe Ala Val Asp Glu Ser Gly Leu Trp
545   550   555   560

Val Ile Tyr Pro Ala Val Asp Glu His Asp Glu Thr Gln His Glu Val
                565   570   575

Ile Val Leu Ser Arg Leu Asp Pro Ala Asp Leu Ser Val His Arg Glu
            580   585   590

Thr Thr Trp Lys Thr Arg Leu Arg Arg Asn Ser Tyr Gly Asn Cys Phe
            595   600   605

Leu Val Cys Gly Ile Leu Tyr Thr Val Asp Thr Tyr Asn Gln His Glu
            610   615   620

Gly Gln Val Ala Tyr Ala Phe Asp Thr His Thr Gly Thr Asp Ala His
625   630   635   640

Pro Gln Leu Pro Phe Leu Asn Glu Tyr Ser Tyr Thr Thr Gln Val Asp
                645   650   655

Tyr Asn Pro Lys Glu Arg Val Leu Tyr Ala Trp Asp Asn Gly His Gln
                660   665   670

Leu Thr Tyr Thr Leu His Phe Val Val
            675   680

<210>   13
<211>   704
<212>   PRT
<213>   Homo sapiens

<400>   13

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Met Ala Ala Ala Ala Leu Pro Pro Arg Pro Leu Leu Leu Leu Pro Leu
1   5   10   15

Val Leu Leu Leu Ser Gly Arg Pro Thr Arg Ala Asp Ser Lys Val Phe
        20   25   30

Gly Asp Leu Asp Gln Val Arg Met Thr Ser Glu Gly Ser Asp Cys Arg
        35   40   45

Cys Lys Cys Ile Met Arg Pro Leu Ser Lys Asp Ala Cys Ser Arg Val
    50   55   60

Arg Ser Gly Arg Ala Arg Val Glu Asp Phe Tyr Thr Val Glu Thr Val
65   70   75   80

Ser Ser Gly Thr Asp Cys Arg Cys Ser Cys Thr Ala Pro Pro Ser Ser
            85   90   95

Leu Asn Pro Cys Glu Asn Glu Trp Lys Met Glu Lys Leu Lys Lys Gln
        100   105   110

Ala Pro Glu Leu Leu Lys Ser Ile Lys Ala Asn Leu Ser Arg Glu Asn
        115   120   125

Glu Val Val Lys Asp Ser Val Arg His Leu Ser Glu Gln Leu Arg His
    130   135   140

Tyr Glu Asn His Ser Ala Ile Met Leu Gly Ile Lys Lys Glu Leu Ser
145   150   155   160

Arg Leu Gly Leu Gln Leu Leu Gln Lys Asp Ala Ala Ala Ala Pro Ala
            165   170   175

Thr Pro Ala Thr Gly Thr Gly Ser Lys Ala Gln Asp Thr Ala Arg Gly
            180   185   190

Lys Gly Lys Asp Ile Ser Lys Tyr Gly Ser Val Gln Lys Ser Phe Ala
        195   200   205

Asp Arg Gly Leu Pro Lys Pro Pro Lys Glu Lys Leu Leu Gln Val Glu
    210   215   220

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Lys Leu Arg Lys Glu Ser Gly Lys Gly Ser Phe Leu Gln Pro Thr Ala
225   230   235   240

Lys Pro Arg Ala Leu Ala Gln Gln Gln Ala Val Ile Arg Gly Phe Thr
            245   250   255

Tyr Tyr Lys Ala Gly Lys Gln Glu Val Thr Glu Ala Val Ala Asp Asn
            260   265   270

Ala Leu Gln Gly Thr Ser Trp Leu Glu Gln Leu Pro Pro Lys Val Glu
            275   280   285

Gly Arg Ser Asn Ser Ala Glu Pro Asn Ser Ala Glu Gln Asp Glu Ala
    290   295   300

Glu Pro Arg Ser Ser Glu Arg Val Asp Leu Ala Ser Gly Thr Thr His
305   310   315   320

Leu Ile Leu Pro Pro His Ser Leu His His His Ser Thr Pro Val Leu
            325   330   335

Ala Thr Pro Ala Pro Phe His Leu Gln Cys His Asn Lys Pro Val Pro
            340   345   350

Ser Pro Arg Arg Trp Gln Thr Thr Pro Ser Arg Ala Leu Pro Gly Trp
    355   360   365

Ser Asn Cys Arg Pro Arg Trp Arg Ala Gly Pro Thr Pro Gln Ser Pro
    370   375   380

Thr Pro Gln Ser Arg Met Arg Leu Ser Pro Gly Pro Pro Ser Glu Trp
385   390   395   400

Thr Trp Leu Leu Ala Pro His Phe Asn Pro Cys His His His Arg
            405   410   415

His Pro His Pro Gln Pro Pro Thr Thr Ser Leu Leu Pro Thr Glu Pro
            420   425   430

Pro Ser Gly Pro Glu Val Ser Ser Gln Gly Arg Glu Ala Ser Cys Glu

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Gly Thr Leu Arg Ala Val Asp Pro Pro Val Arg His His Ser Tyr Gly
    450   455   460

Arg His Glu Gly Ala Trp Met Lys Asp Pro Ala Ala Arg Asp Asp Arg
465   470   475   480

Ile Tyr Val Thr Asn Tyr Tyr Tyr Gly Asn Ser Leu Val Glu Phe Arg
            485   490   495

Asn Leu Glu Asn Phe Lys Gln Gly Arg Trp Ser Asn Met Tyr Lys Leu
            500   505   510
                                    .

Pro Tyr Asn Trp Ile Gly Thr Gly His Val Val Tyr Gln Gly Ala Phe
            515   520   525

Tyr Tyr Asn Arg Ala Phe Thr Lys Asn Ile Ile Lys Tyr Asp Leu Arg
    530   535   540

Gln Arg Phe Val Ala Ser Trp Ala Leu Leu Pro Asp Val Val Tyr Glu
545   550   555   560

Asp Thr Thr Pro Trp Lys Trp Arg Gly His Ser Asp Ile Asp Phe Ala
            565   570   575

Val Asp Glu Ser Gly Leu Trp Val Ile Tyr Pro Ala Val Asp Asp Arg
            580   585   590

Asp Glu Ala Gln Pro Glu Val Ile Val Leu Ser Arg Leu Asp Pro Gly
            595   600   605

Asp Leu Ser Val His Arg Glu Thr Thr Trp Lys Thr Arg Leu Arg Arg
    610   615   620

Asn Ser Tyr Gly Asn Cys Phe Leu Val Cys Gly Ile Leu Tyr Ala Val
625   630   635   640

Asp Thr Tyr Asn Gln Gln Glu Gly Gln Val Ala Tyr Ala Phe Asp Thr
            645   650   655

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His Thr Gly Thr Asp Ala Arg Pro Gln Leu Pro Phe Leu Asn Glu His
        660   665   670

Ala Tyr Thr Thr Gln Ile Asp Tyr Asn Pro Lys Glu Arg Val Leu Tyr
        675   680   685

Ala Trp Asp Asn Gly His Gln Leu Thr Tyr Thr Leu His Phe Val Val
    690   695   700